REMARKS

Election/Restrictions

Applicants thank the Office for withdrawing the species restriction requirement in view of Applicants' arguments in the reply filed on April 8, 2008.

Claim Rejections – 35 U.S.C. § 102

Claims 18 and 22-33 have been rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Fosnaugh and McSwiggen (U.S. 2003/0143732, USSN 10/224,005 ("the '005 application")). Office Action, at page 2. Applicants respectfully traverse and submit herewith a Rule 1.132 declaration by Peter Haeberli, the Patent Attorney who prepared both the '005 application, which published as US 2003/0143732, and the instant application, indicating that the subject matter claimed herein but allegedly disclosed by the '005 application was the invention of James McSwiggen. As such, the pending claims are not anticipated by the disclosures of the '005 application and Applicants respectfully request withdrawal of this rejection.

Claim Rejections – 35 U.S.C. § 103(a)

Claims 18 and 20-33 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Elbashir et al. (2001, EMBO J., v. 20(23):6877-88); Monia et al. (U.S. 6,033,910), Piekin (1991, Science, v. 253:314-7) and Matulic-Adamic, et al. (U.S. Patent 5,998,203). Office Action, at page 5. Applicants traverse.

It is respectfully submitted that, while the Office was correct in stating that Elbashir did not teach all of the instantly claimed modifications and did not teach siRNAs having terminal cap moieties, the Office has neglected to mention another important claimed feature that is clearly missing from the Elbahir reference: that ***at least two of the modifications are different from each other.*** Specifically, whilst Elbashir teaches incorporating 2'-deoxy nucleotides in one or both strands, ***or*** incorporating 2'-O-methyl nucleotides in one or both strands, but ***not both.*** As such, Elbashir does not teach or suggest a single siRNA molecule having at least 2 different modifications.

The deficiency of Elbashir cannot be remedied by the disclosures of the Monia, Piekin or Matulic-Adamic because modifications that were commonly known to ***stabilize*** antisense molecules

(Monia) against nuclease degradation have been reported to be ***detrimental to RNAi activity*** if applied to an siRNA molecule beyond the terminal nucleotides or if at all, by the Elbashir reference cited herein. As such, there was no reasonable expectation that other known chemical modifications, such as those described in Piekin and Matulic-Adamic, can be applied to siRNA molecules without abrogation of RNAi activity, even if those modifications could indeed improve nuclease resistance. Nor was there an expectation that the gapmer motifs of Monia, which allegedly were beneficial to "enhance the stability of antisense molecules" (Office Action, at page 6), would be suitable for an siRNA molecule. There was simply no correlation in the art tying nuclease stability to RNAi activity.

Specifically, Elbashir reported, in no uncertain terms, that 2'-deoxy modification, one of the most commonly used chemical modifications on antisense molecules (*e.g.,* as reported in the Monia reference herein), must be limited to the 3'-terminal overhanging nucleotides and/or the two nucleotides immediately adjacent thereto, and extensive 2'-deoxy modification on an siRNA molecule abrogates activity. Another commonly used chemical modification, 2'-O-methyl (also reported in the Monia reference herein), should not be used at all. *See* Elbashir, at page 6885, left column, lines 7-13:

> ***2'-deoxy substitution of the 2 nt 3'-overhanging ribonucleotides*** do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNAse resistance of siRNA duplexes. ***More extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNA to mediate RNAi,*** probably by interfering with protein association for siRNP assembly.

(*emphasis added*). This is further illustrated in Figure 4 on page 6882, where it is clear that 2 nt 2'-deoxy substitutions at the overhanging nucleotides are tolerated, while 4 nt substitutions are detrimental to RNAi activity; and complete replacement of one or both strands with deoxy or 2'-O-methyl residues "abolished" RNA activity, as the authors have expressly acknowledged. *See* Elbashir, at page 6882, left column, lines 1-4.

It is respectfully noted that Elbashir reports that ***any*** 2'-O-methyl substitution reduces the RNAi activity. In the sentence "[m]ore extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNA to mediate RNAi" (quoted above), the phrase "more extensive" clearly refers to the 2'-deoxy modifications because there are no "less extensive" 2'-O-methyl modifications to compare with in the preceding sentence or in the rest of the Elbashir paper.

As such, Elbashir clearly teaches that 2'-deoxy and 2'-O-methyl modifications, which were ***known to protect antisense molecules against nuclease degradation*** are in fact ***not desirable*** in the siRNA context because they largely cause loss of RNAi activity. If these commonly ***known stabilizing modifications*** are ***detrimental to RNAi activity***, then there is no expectation that other known modifications, such as the 2'-F modification of Monia/Pieken and terminal cap moieties of Matulic-Adamic, and known motifs, such as the gampers of Monia, could be applied to siRNA molecules.

This lack of expectation of success can be easily understood by analogizing to the art of putting out fires. Many types of extinguishing agents, including foam, water, carbon dioxide and dry powder, had been known to be effective in the prior art for putting out common combustible paper/wood fires and flammable liquid kerosene fires. But among these agents, foam and water were reported to be not very effective at putting out another kind of fires caused by combustible metals, although it was not clear how combustible metal fires worked or how they differed from the paper/wood fires or kerosene fires. Those skilled in the art, aware of the ineffectiveness of foam and water on combustible metal fires, would have had ***no reasonable expectation of successfully*** putting out a metal fire if provided with carbon dioxide or dry powder, even though they knew these agents worked well with the first two types of fires. Even if the carbon dioxide and/or dry powder did put out the metal fires, it would not have changed the fact that those skilled in the art had no reasonable expectation of success until they actually tried.

Like the fires, not all nucleic acid-based gene suppressors are created equal. At the time of the present invention, it was known that siRNA molecules are nucleic acid-based molecules, just like antisense and ribozyme molecules, but they suppress gene expression *via* a different mechanism. *See e.g.,* Fire (U.S. 6,506,559, which describes the differences between RNAi by an RNA duplex and gene suppression by antisense and other prior art nucleic acid molecules) (attached herewith). The chemical modifications that had been successfully applied to antisense molecules but found limited or no applicability in the siRNA context are like the foam and water in this analogy, working well with paper/wood and kerosene fires, but have limited effectiveness on metal fires. Rather than providing teaching and suggestion, the foam and water and known modifications such as 2'-deoxy and 2'-O-methyl indicate a lack of predictability and no reasonable expectation of success when it comes to metal fires and siRNA molecules, respectively. There is thus no

reasonable expectation of success with carbon dioxide or dry powder in the fire context, and with the 2'-F modification (Piekin/Monia) and the terminal caps (Matulic-Adamic) in the siRNA context, even though some of these materials/modifications did turn out to be feasible/beneficial.

Therefore, the deficiency of Elbashir cannot be remedied by disclosures of modifications or motifs in the antisense/ribozymes areas, and the instant claims are not rendered obvious by the cited references. As such, Applicants respectfully request withdrawal of the obviousness rejections.

Conclusion

In view of the foregoing, Applicants submit that the claims are in condition for allowance, which is respectfully solicited. If the Examiner believes a telephone conference would expedite prosecution, she is urged to telephone the undersigned at the telephone number below.

Respectfully submitted,

Sirna Therapeutics, Inc.
A Wholly Owned Subsidiary of Merck & Co.

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